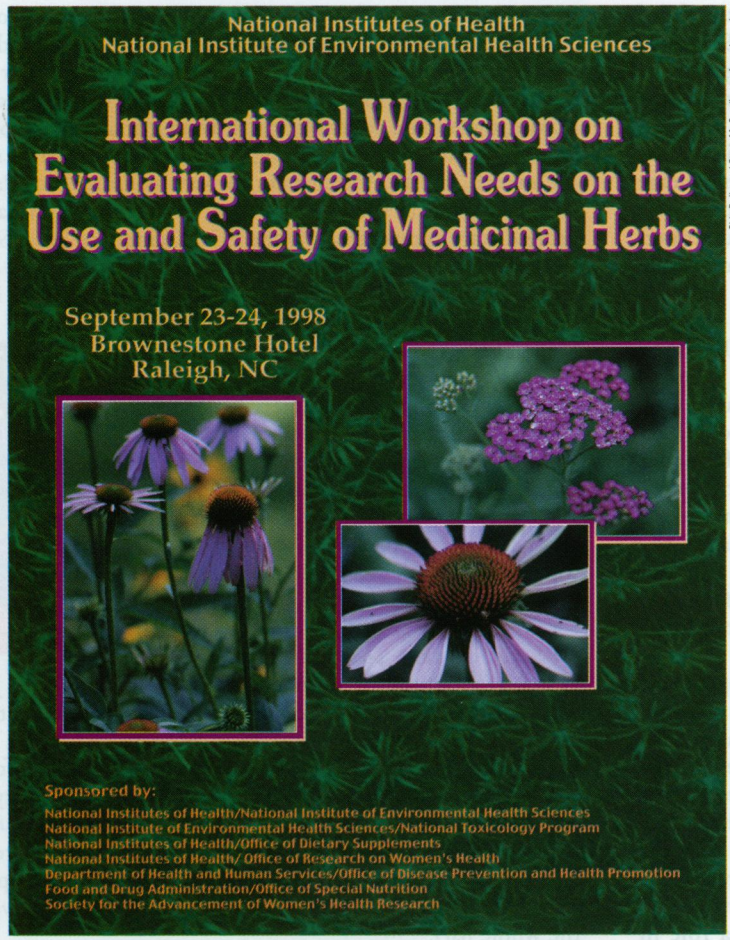
## Herbal Health

Ads for herbal medicines are everywhere these days, encouraging consumers to treat themselves "the natural way" for everything from asthma to hypertension. What do we really know about these products—and what more do we need to learn? These questions were addressed at the International Workshop to Evaluate Research Needs on the Use and Safety of Medicinal Herbs, held 23–24 September 1998 in Raleigh, North Carolina. The workshop was sponsored by the NIEHS, the National Toxicology Program (NTP), the NIH Office of Dietary Supplements, the NIH Office of Research on Women's Health, the Department of Health and Human Services Office of Disease Prevention and Health Promotion, the Food and Drug Administration (FDA) Office of Special Nutrition, and the Society for the Advancement of Women's Health Research.

The workshop was developed to address questions about the availability and quality of toxicological data on medicinal herbs, which are being used in ever increasing numbers in the United States, as well as in other countries. Representatives from research, industry, medical, advocacy, and consumer groups gathered to discuss the use of herbal products, establish what research is needed to address public health concerns, and weigh various strategies for carrying out this research.

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### Who Uses Medicinal Herbs?

According to Phyllis Greenberger, executive director of the Society for the Advancement of Women's Health Research, most U.S. botanical product users are white, college-educated, middle-aged women. Many botanical products are marketed towards women, such as St. John's wort (*Hypericum perforatum*), which is promoted as a treatment for mild depression, a condition that affects two to three times more women than men.

Mark Blumenthal, executive director of the American Botanical Council, a nonprofit education group in Austin, Texas, said that 30% of all U.S. adults use some type of herbal product. Annual product sales are expected to reach approximately $5 billion by the year 2000, and the market is rapidly spreading from specialty and health food stores into pharmacies and grocery stores. Press coverage of herbal remedies has helped fuel their phenomenal rise in popularity. For instance, the news show *20/20* covered an article in the 3 August 1996 issue of the *British Medical Journal* in which analysis of 23 clinical trials on St. John's wort showed the plant to be more effective than placebos in treating depression. After the show was broadcast in June 1997, St. John's wort rocketed from virtual anonymity to being one of the top botanical sellers of 1998.

But a lack of adequate regulation among herbal products leads to a confusing mix of products, offering different dosages and dosing formats, such as capsules, teas, and pills. Greenberger says some of these products are not tested for either purity or potency. Furthermore, each time a consumer purchases a botanical product, it is uncertain whether the product will work, or even contain the advertised amount of active ingredient. Keynote speaker Norman R. Farnsworth, director of the Program for Collaborative Research in the Pharmaceutical Sciences at the University of Illinois at Chicago, cited a study conducted by the Good Housekeeping Institute and presented last March at the First Consumer Safety Symposium on Dietary Supplements and Herbal Remedies. The study looked at 10 popular St. John's wort products, 6 in capsule form and 4 in liquid extract form, and found marked discrepancies—as much as a 17-fold difference—in the levels of the suspected active ingredients contained in the tested products.

### International Use of Medicinal Herbs

Hildebert Wagner, chairman for special pharmacognosy at the Institute for Pharmaceutical Biology in Munich, Germany, described research being done on medicinal plants in Germany, where most herbal products are classified by law as drugs, and must therefore meet the same criteria for quality, efficacy, and safety as synthetic drugs. According to Wagner, approximately 400 single- and double-blind clinical trials have already been conducted with various standardized herbal extracts and mixtures, with promising results. Many of these studies investigated botanicals that are widely used in the United States, such as *Ginkgo biloba*, garlic (*Allium sativum*), and kava kava (*Piper methysticum*).

Commission E was established by the German government in 1978 to evaluate herbal drugs for safety and efficacy. The commission published over 300 monographs, recently translated into English by the American Botanical Council, on a number of individual extracts and botanical mixtures. The monographs include assessments of whether the extracts or mixtures listed are safe and effective for nonprescription use, and also list side effects, contraindications, and dosage ranges. However, the monographs do not reference the sources used in making those assessments, which undermines their credibility in the eyes of many U.S. researchers. It also makes it difficult to evaluate the monographs' statements, conclusions, and recommendations from a scientific perspective.

The European Scientific Cooperative on Phytotherapy (ESCOP) is a voluntary association of medicinal plant experts founded in 1989. ESCOP works to

advance the scientific stature of herbal medicines and assists in harmonizing their regulatory status within European nations. The cooperative publishes monographs summarizing the therapeutic uses of various medicinal plants. Unlike the Commission E monographs, however, the ESCOP monographs do not propose standards or characterize plant extracts.

Sukh Dev, currently a visiting professor at the B.R. Ambedkar Centre for Biomedical Research at the University of Delhi in India, spoke on the ancient Indian tradition of Ayurvedic medicine. This tradition prescribes holistic treatments combining drugs, diet, and exercise, and employs some 1,250 different herbs. Ayurvedic medicine is only one form of traditional medicine that is widely practiced in India, especially among the rural populations. Traditional practitioners may also participate in public health programs such as providing child immunizations and diagnosing prevalent diseases such as malaria and tuberculosis. In Japan, meanwhile, according to Yutaka Sashida, a professor of chemistry at the Tokyo University of Pharmacy and Life Science in Japan, about 85% of doctors combine traditional herbal remedies with modern medicines, and botanical prescriptions are covered by medical insurance.

## Research Needs

***Standardization.*** Most participants named bioactive standardization as the single most pressing research need for herbal medicines. The first step in standardization is determining the biologically active component(s) of each botanical, or some other marker by which to judge product quality. Standardization of medicinal herbs must also cover many other considerations, including the species of plant used, harvest schedule, storage methods, physical characteristics of raw materials, methods for producing uniform extracts, and knowing which part of the plant (e.g., root, flower, leaf) contains the desired bioactive compounds.

Rossanne Philen, an epidemiologist with the Centers for Disease Control and Prevention, stressed the importance of using botanicals within the context of their traditional use. It's easy, she said, to take the approach that "if a tea is good, a concentrated capsule must be 10 times better." Floyd Leaders, chairman and CEO of Botanical Enterprises of Rockville, Maryland, pointed out that many companies have westernized herbal remedies that were once administered as teas or soups into the pills and capsules that seem to be preferred by U.S. consumers—possibly to the detriment of the efficacy of the original product.

***Prioritization of research needs.*** There was little agreement on how to prioritize the plants to be studied. Farnsworth called for a more efficient approach to ranking which plants to study first. "Why study ginseng," he asked, "when it's already been used for 3,000 years [with no apparent side effects]?" But, others countered, from a public health perspective, it makes sense to study those botanicals that are already most widely used and to which the most people will therefore continue to be exposed. Still others claimed that basing studies on the sales of particular products would constitute marketing-driven research.

Some suggested first studying those medicinal herbs that show the most promise for the greatest health impacts. This could include herbs known or suspected to contain toxic ingredients or, alternately, treatments that target widespread health problems such as osteoporosis or arthritis, and serious illnesses for which there currently are no medications. David Schardt, associate nutritionist for the Center for Science in the Public Interest, an education and advocacy organization in Washington, DC, suggested studying botanicals for which "there are already some pieces of the puzzle in place, where just a little more research is needed in order for doctors to be able to recommend these products to patients, or at least to not discourage their use."

***Education for all stakeholders.*** Kenneth D. Fisher, executive director of the Office of Disease Prevention and Health Promotion, said the medical community needs to be better educated on the traditional uses of medicinal herbs. This was pointed up by a study published in the 17 June 1998 issue of the *Journal of the American Medical Association* (*JAMA*) that was cited at the workshop. The study examined the effects of garlic oil on serum lipoprotein concentrations and cholesterol levels, and concluded that "[g]arlic therapy for treatment of hypercholesterolemia cannot be recommended on the basis of this study." The problem? The celebrated cholesterol-reducing effects of the pungent plant come only from eating fresh garlic or the dried powder equivalent—not the garlic oil that was used in the *JAMA* study.

Another misconception was broached by Lois Gold, director of the Carcinogenic Potency Project at the NIEHS Environmental Health Sciences Center at the University of California at Berkeley, who said, "Consumers seem to think herbals are safe just because they are 'natural,' and that synthetic chemicals pose greater health hazards than naturally occurring chemicals." In contrast to this assumption, Gold said, the toxicology of natural and synthetic chemicals is similar, with roughly equal proportions of natural and synthetic chemicals being shown through rodent assays to be carcinogenic. Moreover, said Gold, compared to other chemical exposures, herbal products are taken at doses that are relatively close to their toxic range. They are also often taken chronically.

Other problems identified included haphazard record keeping by gatherers and importers of herbs, and nonstandardized identification techniques, both of which can result in adulterated raw materials. Collectors must be trained to properly identify the raw materials, and must be aware of common substitutes or look-alikes for particular plants, which can contribute to adulteration problems. William R. Obermeyer, a research chemist in the Division of Natural Products at the Center for Food Safety and Applied Nutrition, stated that some patent medicines being imported into the United States, primarily from China, contain potentially toxic substances such as diazepam, camphor, and mercury. Botanicals may also be contaminated with pesticides, excreta, molds, and other adulterants.

With the many thousands of botanicals in use today, it is important to distinguish among the various species of plants. In addition to the myriad of common names for different botanicals (for instance, "boneset," "feverwort," and "thoroughwort" are just three of the nicknames for *Eupatorium perfoliatum*), plants can even have multiple genus/species synonyms. For example, while the accepted binomial for saw palmetto is *Serenoa repens*, the plant is nevertheless frequently referred to as *Sabal serrulata*, and less frequently as *Corypha repens* or even *Brahea serrulata*. Marriott stressed the importance of referring to medicinal herbs by their correct, accepted Latin binomials. She also urged writers in the audience to use the Latin binomials in medical article titles and keywords so the articles can be more easily and reliably retrieved by citation search engines.

***Collaboration.*** Common sense calls for there to be a central organizing body to coordinate research into botanicals—perhaps the Office of Dietary Supplements or the NIEHS. But, said Lori A. Love, director of the Clinical Research and Review Staff with the FDA Center for Food Safety and Applied Nutrition, "Before any research can begin, different fields of scientific expertise, including psychiatry, cardiology, and endocrinology, need to be engaged in order to frame appropriate, pertinent questions."

Blumenthal pointed out that many of the necessary studies on botanicals have been conducted already in Europe. The data

are there, Blumenthal said; it's just a matter of knowing where and how to find them. But Schardt defended the desire to reproduce such studies in U.S. labs, pointing out that, for example, European studies on the efficacy of St. John's wort for treating depression average a length of only five weeks—even though St. John's wort can take as long as four weeks to have any effect. He also asserted that the results of certain studies may not be as compelling as some claim. For instance, in response to a claim that some 28 controlled trials of various forms of echinacea have been conducted in Europe, Schardt said that most of those studies used parenteral echinacea, which is not available in the United States, or proprietary products that also are not available to U.S. consumers. Furthermore, Schardt said, the results of several controlled trials testing the effects of oral echinacea supplements on the common cold and influenza are inconclusive. Still, there was general agreement among the participants that the United States must display more willingness to cooperate with and participate in international research on standardization, efficacy, and safety.

***Financial support.*** Many speakers felt that the money for testing, analyzing, and evaluating the published safety and efficacy data on medicinal herbs should come from the government, and looked to the FDA as the natural choice for initiating such studies. But Yuan-Yuan Chiu, deputy director of the Office of New Drug Chemistry at the FDA Center for Drug Evaluation and Research, claimed the agency has barely enough resources to maintain the programs already in place, and called on the other government agencies represented to share their funds and resources.

Others felt that industry bears the burden of responsibility for supporting research. Pharmaceutical companies routinely spend 10–20% of their profits on research and development, a figure that is not borne out in the botanical industry. But, said Loren Israelsen, executive director of the Utah Natural Products Alliance, contrary to an editorial in the 17 September 1998 issue of the *New England Journal of Medicine* in which editors Marcia Angell and Jerome Kassirer suggest the botanical industry is not interested in research, the industry very much wants to conduct and collaborate on botanicals research.

Israelsen described some of the dilemmas faced by the industry in terms of research incentives versus expenditures. In order to receive FDA approval as a nonprescription drug, each substance within a given plant—not just those within the extract used in the botanical preparation—would need to be studied in a lengthy, expensive process. In addition, the FDA review process for nonprescription drugs does not allow consideration of foreign data. Therefore, many studies that have already been done overseas would need to be duplicated.

Another issue is the Dietary Supplement Health and Education Act of 1994, which for the first time allowed botanical manufacturers to label their products with claims of how the product may affect the structure or functioning of the body. With the passage of the act, many manufacturers began conducting legitimate research in order to formulate their claims, but some manufacturers indulge in "borrowed science"—applying the results of another company's studies to their own products, often leading to inaccurate claims (the resultant mislabeling is addressed under the Federal Food, Drug, and Cosmetic Act). Finally, most synthetic drugs are developed with the goal of being patented. But with the countless varieties of botanical products being sold, it is impossible to claim market exclusivity as a research incentive.

### Botanicals Today . . . and Tomorrow

Research and regulatory decisions are much too complex to base on a single workshop. However, most participants seemed satisfied to have been able to voice the concerns of their particular camps, and excited about the evident—albeit fragmented—wealth of expertise represented at the workshop. A summary of several recommendations drawn from workshop presentations and discussions is being compiled by the NIEHS. Of the workshop, co-organizer H.B. Matthews said, "We've certainly set the stage for a continuing dialogue on this subject."

According to Israelsen, a "broad understanding among all interested parties of the issues involved" is needed. "We need to serve the consumer, set aside animosities, and just do the work," he said. "The real [goal] is that the consumers have safe botanical products.

## Autoimmune Disease and the Environment

According to a study published in the September 1997 issue of *Clinical Immunology and Immunopathology* by scientists at The Johns Hopkins University in Baltimore, Maryland, at least 10 million people in the United States are affected by one of 80 known autoimmune diseases. These diseases include both organ-specific conditions, such as type I diabetes, and system-wide diseases, such as systemic lupus erythematosus. They range from the well-known, such as multiple sclerosis, to the relatively rare and obscure, such as Takayasu's arteritis (which attacks the aorta and its branches). Perhaps because of the wide range of the health effects caused by these diseases, little is known about their origin and epidemiology.

In an effort to address the dearth of etiologic information on this mysterious family of diseases, a workshop entitled Linking Environmental Agents and Autoimmune Diseases was held 1–3 September 1998 at the NIEHS campus in Research Triangle Park, North Carolina. The workshop was jointly sponsored by the NIEHS, the EPA National Health and Environmental Effects Research Laboratory (NHEERL), the NIH Office of Rare Diseases, the NIH Office of Research on Women's Health, the National Institute of Allergy and Infectious Disease, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Arthritis, Musculoskeletal, and Skin Diseases, the American Autoimmune Related Diseases Association, and the Juvenile Diabetes Foundation.

Almost all autoimmune diseases occur more often in women than in men; in some of these diseases, more than 90% of patients are female. It is not clear exactly why women are targeted more often than men, but estrogen is suspected to play a pivotal role. Autoimmune diseases seem to particularly attack connective tissue and the neuromuscular, endocrine, and gastrointestinal systems, but are not unknown in other parts of the body.

Autoimmunity occurs when the body's immune system turns against itself. The immune system is designed to protect the body by producing antibodies in response to invading microorganisms such as viruses or bacteria. Sometimes, for reasons that are still not fully understood, these antibodies are directed against self-, rather than foreign, antigens. Such a response probably occurs naturally in most peop le to some extent, but for someone with a genetic predisposition to autoimmune disease, bacteria, viruses, toxic agents, or certain drugs may provide the boost necessary to trigger a full-fledged autoimmune response. Other factors that are believed to influence the development of autoimmune disease include age, gender, and reproductive status (e.g., pregnancy).

The workshop drew over 100 scientists from a variety of disciplines, serving as a forum for immunologists, developmental biologists, autoimmune specialists, epidemiologists, molecular biologists, and toxicologists to define the state of the science, identify data gaps, and map out the research still